

ORIGINAL RESEARCH

Estimating the Costs of Therapy in Patients with Relapsed and/or Refractory Multiple Myeloma: A Model Framework

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BACKGROUND: Multiple myeloma is a progressive cancer for which there is no cure. Despite treatment, almost all patients eventually experience periods of disease relapse and remission. With the increasing use of novel therapies, including bortezomib, lenalidomide, carfilzomib, pomalidomide, and panobinostat, benchmarks for assessing the value of these therapies in treating patients with relapsed or refractory multiple myeloma (RRMM) are needed for physicians and payers alike.

OBJECTIVES: To develop a model framework and to calculate an annual estimate of the total costs per patient for the treatment of patients with RRMM using 7 common treatment regimens, including bortezomib plus dexamethasone; panobinostat, bortezomib, and dexamethasone; lenalidomide plus dexamethasone; lenalidomide, bortezomib, and dexamethasone; carfilzomib; carfilzomib, lenalidomide, and dexamethasone; and pomalidomide plus dexamethasone.

METHODS: The expenditures for drugs and their administration, for prophylaxis and adverse event monitoring, and for the treatment of grade 3 or 4 adverse events were included in the calculations of the total pharmacy and medical costs. The drug costs were based on published pricing and labeled dosing schedules; the adverse event prophylaxis and monitoring costs were obtained from peer-reviewed publications; and the adverse event incidence rates were obtained from each regimen's prescribing information and from clinical trials. All the costs were summed over the duration of therapy for which the drugs were administered and were calculated separately for commercial and Medicare plans. The duration of therapy for each regimen was the time for which a patient had to be receiving the regimen to obtain 12 months of progression-free survival based on the duration-of-therapy to progression-free survival ratio observed from published clinical trials and/or the drug's labeling.

RESULTS: The pharmacy costs were highest for pomalidomide plus dexamethasone, whereas the medical costs were highest for the combination of carfilzomib, lenalidomide, and dexamethasone. The total cost associated with available treatments for RRMM was highest for regimens that included lenalidomide (approximate range, \$126,000-\$256,000). Only bortezomib plus dexamethasone and the combination of panobinostat, bortezomib, and dexamethasone had total costs that were lower than \$125,000 per patient.

CONCLUSION: This study represents the first model developed to comprehensively estimate the costs of managing RRMM with all currently approved and guideline-recommended regimens in the United States. As such, it provides the framework and basis for further budget impact analyses and for cost-effectiveness comparisons with these regimens.

KEY WORDS: costs, progression-free survival, relapsed/refractory multiple myeloma, histone deacetylase inhibitor, proteasome inhibitor, immunomodulatory drug, model framework

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Multiple myeloma is a malignant B-cell neoplasm of terminally differentiated plasma cells that accumulate in the bone marrow and frequently invade the adjacent bone, leading to bone destruction and marrow failure.^{1,2} Multiple myeloma accounts for 10% of all blood cancers³ and 1.6% of all new cancer cases in the United States.⁴ Among the general population, the lifetime risk for multiple myeloma is 0.7%.⁴

Multiple myeloma has no cure and, despite treatment, almost all patients experience periods of relapse and remission.¹ Relapsed multiple myeloma is defined as disease that has previously responded to therapy and subsequently progressed beyond 60 days of the last therapy.⁵ Refractory multiple myeloma is defined as “disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of last therapy.”⁵ For patients with relapsed or refractory multiple myeloma (RRMM), there is no published standard of care. Treatment guidelines for RRMM offer many therapeutic options; as such, a wide variety of anticancer regimens and sequencing patterns are used in the real-world clinical practice.²

Novel agents approved for the treatment of RRMM—including bortezomib, a proteasome inhibitor; carfilzomib, a second-generation proteasome inhibitor; and lenalidomide and pomalidomide, which are immunomodulatory drugs (IMiDs)—are used at different points throughout the course of treatment.⁶ In US clinical practice, regimens based on bortezomib form the cornerstone of therapy for multiple myeloma, and bortezomib is used as either first-line therapy or for retreatment in patients who had achieved a durable response before disease relapse.⁷

Similarly, treatment with lenalidomide in induction and as maintenance therapy has gained widespread use.⁸ With each successive line of treatment, however, therapeutic options become increasingly limited, and patients experience lower rates of clinical response and shorter progression-free survival (PFS); that is, the time between the start of treatment and progressive disease or death, on each subsequent disease relapse.^{9,10}

The total direct medical costs associated with cancer treatment in the United States were estimated to be \$124.6 billion in 2010.¹¹ Multiple myeloma accounts for a small percentage (1%) of all patients with cancer¹²; however, the associated costs over the course of the disease may be disproportionately high compared with other cancers that have metastasized to the bone.¹³ Moreover, these costs are expected to rise with the aging of the US population and with extended patient survival from newer and improved therapies.

Improvements in available treatment regimens have enabled patients with RRMM to live longer, and overall survival has increased from a median of 4.6 years in 2001-2005 to 6.1 years in 2006-2010.¹⁴ Patients are liv-

KEY POINTS

- Almost all patients with multiple myeloma, a progressive cancer for which there is no cure and no standard of care, experience periods of disease relapse despite treatment.
- This is the first US model to comprehensively estimate the costs of treatment for relapsed or refractory multiple myeloma (RRMM) based on all currently approved and guideline-recommended regimens.
- The analysis focused on the annual per-patient treatment cost with 7 regimens.
- The pharmacy and medical costs were highest for regimens that included lenalidomide (approximate total cost range, \$126,000-\$256,000).
- Only bortezomib plus dexamethasone and the combination of panobinostat, bortezomib, and dexamethasone had total per-patient treatment costs of <\$125,000.
- Bortezomib plus dexamethasone had the lowest annual per-patient cost (\$90,616); carfilzomib plus lenalidomide and dexamethasone had the highest (\$256,416) in commercially insured patients.
- The total treatment cost was highest (\$148,326) for the combination of carfilzomib, lenalidomide, and dexamethasone in patients with commercial insurance.
- The total pharmacy cost was highest (\$135,774) for pomalidomide plus dexamethasone.
- This study provides a framework that can be used for further budget impact analyses and cost-effectiveness comparisons with these regimens.

ing longer because they are receiving more lines of therapy and are achieving longer PFS. More lines of therapy, however, result in greater costs per patient, especially because physicians are prescribing newer therapies that are, in most cases, more expensive. As survival in patients with RRMM is extended and treatment is prolonged, the costs of therapy have become increasingly important to payers and to patients.¹⁵

Although drug costs form a conspicuous portion of treatment costs in multiple myeloma, myeloma-related healthcare costs are also significantly driven by disease complications, which result in inpatient hospitalizations, hospital readmissions, and medical procedures.^{12,16,17} For example, the Healthcare Cost and Utilization Project Nationwide Inpatient Sample found an estimated mean cost of \$28,700 per patient with multiple myeloma per hospital stay (among the highest of all cancers) and a

Table 1 Reported Median Duration of Therapy to Achieve 12 Months of Progression-Free Survival

Regimen/source of data	Median DOT, mo	Median PFS, mo	DOT to yield 12 months of PFS, mo
Panobinostat, bortezomib, dexamethasone ^{22,23}	5.0	12.0	5.0
Bortezomib + dexamethasone ^{22,23}	6.1	8.0	9.2
Lenalidomide + dexamethasone ²⁴	10.1	11.1	10.9
Lenalidomide, bortezomib, dexamethasone ²⁵	8.0	9.5	10.1
Carfilzomib, lenalidomide, dexamethasone ²⁶	20.5	26.3	9.4
Carfilzomib ²⁷	3.0	3.7	9.7
Pomalidomide + dexamethasone ^{28,29}	3.7	4.0	11.1
DOT indicates duration of therapy; PFS, progression-free survival.			

total cost of \$522 million (based on 18,200 discharges) in 2009.¹⁸ Moreover, the average length of hospital stay (mean, 11.6 days) associated with multiple myeloma was among the longest of the cancers that were evaluated,¹⁸ and 28.4% of patients who were hospitalized were readmitted within 30 days of their initial hospitalization.¹⁶ Thus, the avoidance of hospitalizations may be an important approach to control costs in this disease and to enhance patient lives.

Prolonging the duration of remission and/or lengthening PFS are the primary goals of therapy for patients with multiple myeloma and may lead to the avoidance of hospitalizations and other outcomes associated with significant costs.¹⁰ Patients often experience their best response to novel agents when they are used early in the course of therapy after the first disease relapse; however, retreatment with bortezomib or an IMiD after the first relapse with the same regimen or in combination with other drugs has demonstrated efficacy.¹⁰

Two trials—VISTA¹⁹ and RETRIEVE²⁰—successfully demonstrated overall response rates (ie, at least a partial response) of 47% and 40% for patients with previous bortezomib exposure and subsequent retreatment, respectively. The response rates observed were not significantly different from the overall response rates that were seen in the respective bortezomib-naïve arms.

Thus, an attractive option after a second relapse, particularly in patients who were previously exposed to

bortezomib and an IMiD and who are being considered for retreatment with bortezomib, may be the addition of a drug with a novel mechanism of action in combination with other agents. This approach may mitigate the tangible direct medical costs and the intangible, and both-ersome, effects of disease progression and its treatment.

To understand the costs of treatment across the current spectrum of regimens for patients with RRMM, a Microsoft Excel-based treatment regimen cost estimator was developed. A review of published studies in 2011 found that, despite advances in therapy for multiple myeloma, the literature at the time was still lacking economic comparisons of novel therapies, specifically cost-effectiveness studies.²¹ Since that time, 1 study evaluating the costs of care of multiple myeloma has been published.¹⁵ Durie and colleagues developed an economic model to evaluate the total treatment costs and the monthly costs without progression associated with lenalidomide plus dexamethasone (Rd) versus bortezomib plus dexamethasone.¹⁵ The results of this model demonstrated that the drug and medical costs associated with bortezomib were more than \$17,000 higher than those for patients treated with lenalidomide.¹⁵

Although these results provided a baseline for comparison, the model did not include any treatment regimens that were more recently approved for RRMM (specifically panobinostat, carfilzomib, and pomalidomide), and it contained a limited list of adverse events. To address these gaps, the treatment regimen cost estimator described in this article was developed.

The objectives of this article are (1) to describe the framework of the cost estimator in terms of the cost inputs, assumptions, and calculations; and (2) to calculate the estimated total Medicare and commercial payer cost per patient to achieve 12 months of PFS with US Food and Drug Administration (FDA)-approved and/or National Comprehensive Cancer Network (NCCN)-recommended therapies for RRMM.

Methods

Treatment Regimens and Clinical Inputs

An Excel-based treatment regimen cost estimator was developed with the primary objective of estimating the costs of treatment with RRMM regimens from US commercial and Medicare perspectives. All costs are reported in 2015 US dollars either directly or inflation adjusted from earlier estimates using the medical component of the US Bureau of Labor Statistics Consumer Price Index. The treatment regimens considered were approved by the FDA or were recommended by the NCCN, or involved therapies used in real-world settings for RRMM.

These include the combination of panobinostat, bortezomib, and dexamethasone; bortezomib plus dexamethasone; and lenalidomide plus dexamethasone.

Table 2 Total Number of Doses During the Course of Treatment to Attain 12 Months of Progression-Free Survival

Drug dose	PAN, BTZ, DEX, N	BTZ + DEX, N	LEN + DEX, N	LEN, BTZ, DEX, N	CFZ, LEN, DEX, N	CFZ, N	POM + DEX, N
Panobinostat 20 mg	45						
Bortezomib 1.3 mg	30	43		46			
Dexamethasone 10 mg		86	80	28			
Dexamethasone 20 mg	60			64			
Dexamethasone 40 mg					76		48
Lenalidomide 15 mg				210			
Lenalidomide 25 mg			252		217		
Carfilzomib 20 mg					2	6	
Carfilzomib 27 mg					60	58	
Pomalidomide 4 mg							252

BTZ indicates bortezomib; CFZ, carfilzomib; DEX, dexamethasone; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide.

methasone; Rd; lenalidomide, bortezomib, and dexamethasone (RVD); and the combination of carfilzomib, lenalidomide, and dexamethasone (CRd). Although they were used later in treatment and among patients with a worse prognosis and previous exposure to a proteasome inhibitor and IMiD based on their FDA-approved label, carfilzomib monotherapy and pomalidomide plus dexamethasone were also considered in the cost analysis.

The costs for a drug (oral or intravenous) and its administration (intravenous only), adverse event prophylaxis and monitoring costs, and grades 3 and 4 adverse event costs (monthly rate of therapy multiplied by the costs of treatment) were summed over the duration of a treatment interval to calculate the total costs.

The total costs of therapy per patient were calculated using the total duration of therapy that was theoretically needed to achieve 12 months of PFS. The 12-month time horizon was chosen to reflect the typical budgetary interval for hospitals or for pharmacies. The total time of therapy duration was calculated based on the ratio of median duration of treatment to median PFS. To calculate the costs that are relevant to a typical 1-year payer time horizon, the model assumes that after completing a course of therapy at the median duration of therapy, patients remain without disease progression until reaching the median PFS that was reported in the pivotal clinical trial for each drug or treatment regimen. The patients are then assumed to be subsequently retreated with the same regimen.

This method of determining time duration of therapy was chosen to allow for fair comparisons across the treatment regimens with large variability in PFS (range, 3.7–23.6 months), although this may not always be the case in a real-world clinical setting. In addition, in any typical 12-month period, some patients will begin therapy,

whereas others may be mid-regimen or may be carried over from the previous year. As such, the total duration of therapy theoretically needed to achieve 12 months of PFS based on the median duration of therapy and the PFS reported from pivotal clinical trials of the respective regimens was assumed to be a fair and balanced representation of the duration for which an average or typical patient can be assumed to continue using therapy in a given year.

The data on PFS and duration of therapy were obtained from published clinical trials and/or from drug labeling information and are presented in **Table 1**, along with the total number of months required to obtain a PFS of 12 months.^{22–29}

Drug Costs

The costs for each drug and its administration were calculated as the sum of the total cost per dose over the duration of therapy. The costs to commercial and Medicare plans for oral drugs were based on their wholesale acquisition costs as reported in *Red Book*.³⁰ For drugs administered by intravenous infusion, the Medicare drug cost was based on the average sales price plus 6%,³¹ whereas for commercial intravenous drugs, the cost was estimated at 123.5% of the Medicare cost.³² The Medicare cost for each agent was \$6860 per package of 6 capsules for panobinostat, \$2134 per vial of bortezomib, \$9855 per package of 21 capsules for lenalidomide, \$2392 per vial for carfilzomib, \$11,414 per package of 21 capsules for pomalidomide, and \$11 per package for dexamethasone.

The medical costs related to intravenous drug administration, hydration, and physician office visits were included. The costs of administration were estimated from *Current Procedural Terminology* (CPT) code 99212 (level

Table 3 Costs of Adverse Event Prophylaxis and Monitoring

Prophylactic therapy	Applicable treatment regimens	Cost, \$ ^a	Cost source
IV hydration	Bortezomib- and carfilzomib-containing regimens	57.92 (Medicare) 71.53 (commercial)	References 18, 19
Electrocardiogram	Panobinostat- and carfilzomib-containing regimens	17.16 (Medicare) 21.19 (commercial)	References 18, 19
Herpes zoster	Bortezomib- and carfilzomib-containing regimens	5.34 weekly Acyclovir (400 mg twice daily)	Cost based on WAC of \$0.3814 per tablet ¹⁷
Deep-vein thrombosis/pulmonary embolism	Lenalidomide-containing regimens	22.00 weekly Enoxaparin (40 mg daily)	Cost based on WAC of \$220 per 10 syringes ¹⁷
Renal toxicity, tumor lysis syndrome	Carfilzomib-containing regimens	2.20 weekly Allopurinol (200 mg daily)	Cost based on WAC of \$31.41 per 100 allopurinol 100-mg tablets ¹⁷
Infusion reactions	Carfilzomib-containing regimens	0.11 per carfilzomib dose Dexamethasone (4 mg per carfilzomib dose)	Cost based on WAC of \$11.41 per 4 100-mg tablets ¹⁷
^a Inflation adjusted to 2015 US dollars. IV indicates intravenous; WAC, wholesale acquisition cost.			

2 established office visit) and CPT code 96409 (chemotherapy administration, intravenous push, single drug). The costs included for Medicare and commercial insurance calculations were \$43.98 and \$54.31, respectively, for physician office visits; \$111.20 and \$137.33, respectively, for intravenous administration; and \$57.92 and \$71.53, respectively, for the intravenous administration of hydration.

The model accounted for typical conventions for patient cost-sharing by using a tier 4 copayment rate of \$100 for orally administered drugs (ie, panobinostat, lenalidomide, and pomalidomide). A 20% coinsurance was assumed for drugs administered intravenously (ie, carfilzomib and bortezomib). Cost-sharing for dexamethasone was assumed to be tier 1 at a rate of \$10.³⁰

The number of drug doses over the duration of therapy was calculated based on the dosing schedules provided in the drug's prescribing information or in a pivotal clinical trial for each drug for the base case reported here.

Table 2 illustrates the base-case number of administered doses of each drug by treatment regimen over the duration of therapy needed to achieve 12 months of PFS. Patients were assumed to be adherent to all therapies over the entire duration of therapy, with no skipped doses, dose escalation, or de-escalation. The median duration of therapy was selected, because it is frequently reported in clinical trials, as well as to account for variability in patient adherence that may be expected in real-world settings.

Cost of Prophylaxis and Adverse Event Monitoring

The costs of prophylaxis and monitoring for adverse events are provided in **Table 3**. Specific adverse event prophylaxis measures and monitoring procedures were recommended for some treatment regimens, and a complete blood count with autodifferential was included for all regimens¹⁵ at a cost of \$48.14 for Medicare and \$59.45 for a commercial plan. The costs associated with medical services, such as intravenous hydration, electrocardiogram, and the management of adverse events, were taken from published literature and were inflated to 2015 US dollars (Table 3).

Cost of Adverse Events

The costs related to grade 3 or 4 adverse event profiles for each regimen were calculated using the adverse event rates collected from clinical trials and from the drug labels (**Table 4**). The adverse events considered were those occurring in $\geq 5\%$ of the treatment arm of any regimen, as was reported in each drug's prescribing information or in a pivotal clinical trial. In addition, the costs related to monitoring for arrhythmia and atrial fibrillation were included for panobinostat-, lenalidomide-, and carfilzomib-containing regimens. The unit costs for adverse events were obtained from published sources and were inflated to 2015 US dollars using the medical care component of the US Bureau of Labor Statistics Consumer Price Index.³³

Because the median duration of exposure differs across studies, the adverse event rates were first standardized to

Table 4 Grade 3 or 4 Adverse Event Rates (Monthly Incidence) and Unit Costs

Grade 3 or 4 adverse event	Unit cost, ^a \$	Treatment regimen					
		Panobinostat, bortezomib, dexamethasone	Bortezomib + dexamethasone	Lenalidomide + dexamethasone	Lenalidomide, bortezomib, dexamethasone	Carfilzomib, lenalidomide, dexamethasone	Pomalidomide + Carfilzomib dexamethasone
		Monthly events during therapy, %					
Deep-vein thrombosis/pulmonary embolism	31,645	0.00	0.00	1.19	0.25	0.09	0.00
Pneumonia	14,855	2.52	1.69	0.83	0.00	0.00	4.93
Febrile neutropenia	13,261	0.20	0.08	0.22	0.00	0.00	0.64
Renal failure	12,316	0.10	0.00	0.00	0.00	0.16	1.34
Vomiting	11,934	1.46	0.21	0.17	0.00	0.00	0.00
Nausea	11,934	1.10	0.09	0.17	0.00	0.00	0.14
Dyspnea	10,886	0.47	0.39	0.00	0.00	0.14	2.68
Back pain	10,728	0.16	0.22	0.00	0.00	0.00	1.91
Diarrhea	9738	5.10	1.31	0.30	0.38	0.19	0.21
Asthenia/fatigue	8437	4.78	1.96	0.66	0.59	0.37	5.17
Arrhythmia/atrial fibrillation	6998	0.60	0.00	0.36	0.39	0.00	0.00
Upper respiratory infection	5220	0.47	0.26	0.14	0.00	0.00	0.36
Hypokalemia	1707	3.60	1.15	0.47	0.00	0.46	0.00
Herpes zoster	1287	0.20	0.31	0.00	0.00	0.00	0.00
Hypocalcemia	1155	1.00	0.33	0.36	0.00	0.00	0.19
Anemia	971	3.60	3.13	0.96	0.25	0.83	4.50
Hypomagnesemia	924	1.00	0.16	0.00	0.00	0.00	0.00
Urinary tract infection	901	0.00	0.00	0.14	0.00	0.00	1.72
Peripheral neuropathy	783	3.52	2.39	0.14	0.38	0.13	0.00
Hyperglycemia	166	0.00	0.00	0.00	1.17	0.00	0.00
Hyponatremia	166	2.60	1.15	0.00	0.98	0.00	0.00
Hypophosphatemia	166	4.00	1.97	0.25	1.17	0.00	0.00
Leukopenia	166	4.60	1.31	0.39	1.17	0.00	2.10
Lymphopenia	166	10.76	6.65	0.27	0.00	0.00	1.50
Neutropenia	166	6.90	1.87	3.25	3.75	1.44	9.21
Thrombocytopenia	166	13.48	5.15	1.19	2.75	0.81	4.07

^aInflation adjusted to 2015 US dollars.

a monthly percentage (based on the observed rates during the course of treatment reported in the clinical trials) and were then multiplied by the median duration of therapy for each treatment regimen (Table 1). The model assumes that grade 3 or 4 adverse events occur with equal distribution of risk across the duration of ther-

apy (ie, adverse events are equally likely to occur at any given week of therapy).

Results

The drug costs, medical costs, and grade 3 or 4 adverse event prophylaxis and management costs associated with each treatment regimen are shown in **Table 5**. From the commercial payer perspective, the costs for prophylaxis and the management of grade 3 or 4 adverse events were highest for carfilzomib monotherapy (\$21,670) and for combination therapy with pomalidomide and dexamethasone (\$24,372).

The medical costs were highest for the CRd treatment regimen (\$148,326), whereas 2 regimens (Rd, and pomalidomide plus dexamethasone) incurred no medical costs.

The pharmacy costs were highest for pomalidomide plus dexamethasone (\$135,774) and were lowest for bortezomib plus dexamethasone (\$6), followed by the combination of panobinostat, bortezomib, and dexamethasone (\$33,804). The pharmacy costs for lenalidomide-based regimens ranged from \$97,554 (RVD) to \$117,069 (Rd). All carfilzomib-related costs were medical, and therefore there were no pharmacy costs.

The total cost per patient and the monthly total cost per patient receiving treatment are presented in **Figure 1** and **Figure 2** for the commercial and Medicare plans. The pharmacy and medical costs were highest for regimens that included lenalidomide. The lowest-cost lenalidomide-based therapy was Rd at \$126,153 (commercial) and \$125,976 (Medicare).

The total cost per patient over the course of 12 months of PFS ranged from approximately \$90,600 (bortezomib plus dexamethasone) to approximately \$260,000 (CRd).

Bortezomib and dexamethasone had the lowest total annual cost per patient per 12 months of PFS gained at \$90,616; the combination of panobinostat, bortezomib, and dexamethasone followed at \$118,745.

The total monthly cost per patient receiving therapy (eg, the number of months to achieve 12 months of PFS; Table 1) was highest from the commercial plan perspective for CRd at \$27,422 and was lowest for bortezomib plus dexamethasone at \$9903.

For the Medicare plan, the highest monthly cost per patient receiving therapy was for carfilzomib (\$24,293), and the lowest cost was for bortezomib plus dexamethasone (\$8175).

Discussion

This study presents a framework and foundation for estimating the economic impact of novel therapies for the management of RRMM. Although this model adopted a similar approach to a previously published cost study

Table 5 Total Cost of Treatment Regimens (per Patient) in Medicare and Commercial Health Plans

Regimen	Cost inputs ^a		
	Pharmacy, \$	Medical, \$	Grade 3 or 4 adverse event prophylaxis and management, \$
Commercial			
Panobinostat, bortezomib, dexamethasone	50,704	55,805	12,236
Bortezomib + dexamethasone	6	79,988	10,623
Lenalidomide + dexamethasone	117,069	0	9083
Lenalidomide, bortezomib, dexamethasone	97,554	85,568	6161
Carfilzomib, lenalidomide, dexamethasone	100,811	148,326	7279
Carfilzomib	0	136,878	21,670
Pomalidomide + dexamethasone	135,774	0	24,372
Medicare			
Panobinostat, bortezomib, dexamethasone	50,704	45,187	11,855
Bortezomib + dexamethasone	6	64,768	10,024
Lenalidomide + dexamethasone	117,069	0	8906
Lenalidomide, bortezomib, dexamethasone	97,554	69,286	5507
Carfilzomib, lenalidomide, dexamethasone	100,811	120,102	6240
Carfilzomib	0	110,833	20,599
Pomalidomide + dexamethasone	135,774	0	24,176

^aTotal costs based on data that were either reported in or inflation adjusted to 2015 US dollars.

Figure 1 Cost Estimation Model Total: Cost Comparisons for Treatment Regimens for Relapsed or Refractory Multiple Myeloma in Medicare and Commercial Health Plans

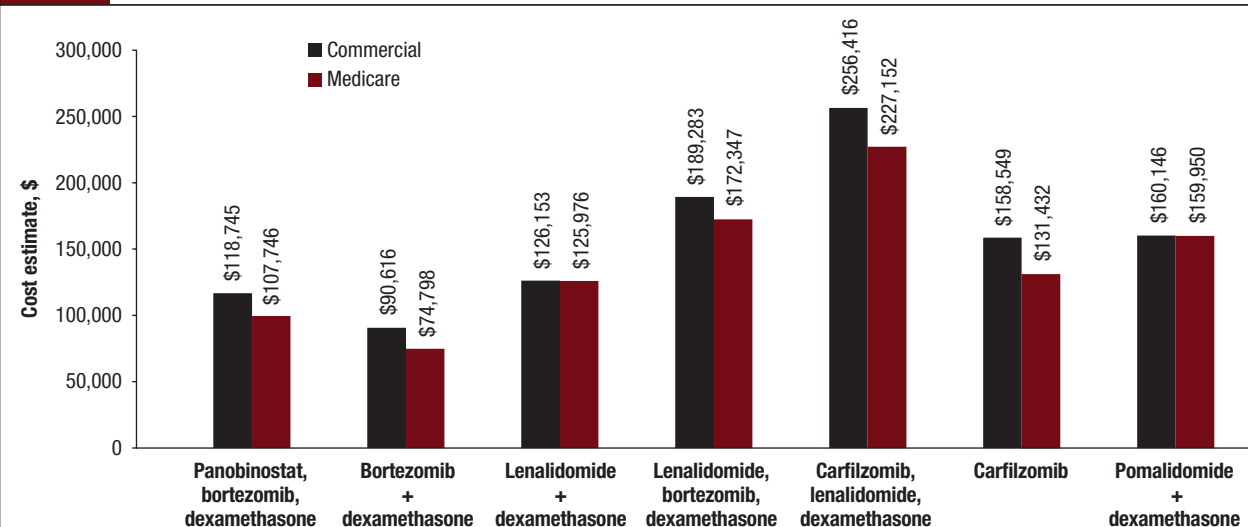
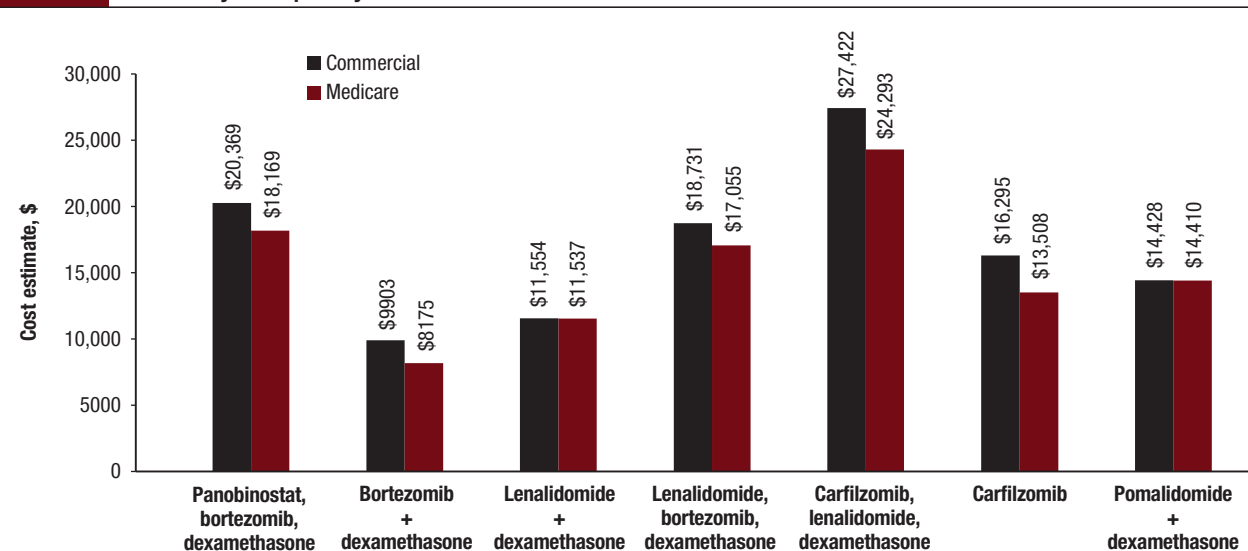


Figure 2 Cost Estimation Model: Total Costs per Patient per Month with Treatment Regimens for Relapsed or Refractory Multiple Myeloma in Medicare and Commercial Health Plans^a



^aMonthly cost per patient receiving therapy is the total cost divided by the median duration of therapy needed to obtain 12 months of progression-free survival.

in patients with RRMM,¹⁵ it builds on the existing literature by evaluating all the frequently used regimens, and by incorporating a broader list of adverse events within a single framework.

Many of the cost and resource components that were included in our study are the same as those previously evaluated, including drug costs, medical costs (ie, prophylaxis, monitoring), and grade 3 or 4 adverse event costs.

The specific adverse events considered from one study to the next were generally the same; however, as new therapies and combination regimens have emerged, the adverse event profile has changed, necessitating a broader inclusion of potentially relevant adverse events to consider when evaluating the total cost.

Our model projected a total 1-year cost for Rd of approximately \$126,000 for Medicare and commercially

insured patients, representing a monthly therapy cost of approximately \$11,500. In the previous cost study, the total 1-year cost of treatment with Rd was estimated at \$103,871 in 2011 US dollars (\$116,295 when inflated to 2015 US dollars using the medical care component of the Consumer Price Index).¹⁵ This is lower than our estimate of \$126,153 (2015 US dollars), a difference that was primarily driven by an increase in cost for lenalidomide since the study was published and by the choice of using wholesale acquisition cost in our study (\$465 daily) versus average wholesale price minus 16% (\$360 daily) as in the previous analysis.

The previous analysis also calculated the monthly cost without progression and showed generally similar results to our analysis when the difference in the estimated price of lenalidomide is considered (\$8949 for Rd and \$10,105 for bortezomib plus dexamethasone), even when using median time to progression (where deaths are censored observations) rather than median PFS (including progression and death as outcomes, leading to a more conservative estimate of efficacy) to inform this calculation.

Another study evaluating an administrative claims database showed a monthly cost estimate of \$6911 for Rd in 2010 US dollars (\$7964 in 2015 US dollars).³⁴ The higher costs in our model may result from including a more robust adverse event profile and increased drug, pharmacy, and medical costs since the publication of the previous studies. The lower costs may reflect the study's design elements; administrative claims analyses, such as that carried out by Binder and colleagues,³⁴ may not capture all of the clinically relevant adverse events (eg, fatigue or nausea).

The duration of therapy to PFS ratio is one method to determine regimen value relative to its cost. A lower-cost treatment regimen combined with a lower duration of therapy to PFS ratio would be valuable from a payer budget perspective. Thus, to assess the relative value of therapies with very different duration of therapy and PFS profiles, the total costs of therapy were determined over an interval that was potentially relevant to payers and physicians alike: the number of treatment months necessary for a patient to remain free of disease progression for 12 months.

The comparison of new therapies for RRMM by their cost per unit of clinical outcome (in this case, 12 months of PFS) allows for fair comparisons across the treatment regimens for several reasons. The median PFS is a generally reported primary or secondary clinical end point, and the median duration of therapy is often reported for clinical trials. Because PFS is a common outcome reported across all comparator regimens, using the PFS to duration of therapy ratio was deemed to be a representative way of standardizing across multiple diverse treatments

to estimate the total patient costs.³⁵⁻³⁷ Moreover, the only other recent cost analysis of RRMM presented the monthly cost of PFS to provide a balanced comparison across the regimens.¹⁵

Second, there exists a large variability in median PFS (range, 8.0-23.6 months) and median duration of therapy (range, 3.0-20.5 months), which was adjusted in our analysis by estimating the number of treatment months required to achieve 12 months of PFS.

Finally, a smaller duration of therapy to PFS ratio also implies the potential for a longer overall treatment-free interval. A longer treatment-free interval may translate into less treatment-related toxicity and fewer treatment-related adverse events and medical visits, in turn resulting in an improved patient experience and value from the healthcare that is delivered.³⁸⁻⁴⁰

Limitations

As with any modeling study, there are several limitations to this research that should be considered. First, the model uses data derived from clinical trials, including duration of therapy, treatment adherence, and dosing schedules, that may differ in a real-world practice. In addition, in clinical practice, patients will be free of progression for intervals that are shorter or longer than the 12 months used in our model. Moreover, the heterogeneity of populations between trials may affect the observed duration of therapy and PFS. For example, in the pomalidomide and carfilzomib monotherapy trials, patients were required to have previously failed a proteasome inhibitor and an IMiD, which represents a population with a worse disease prognosis in comparison to the trials of panobinostat or lenalidomide (patients received between 1 and 3 previous treatment regimens and were not required to have failed previous treatment with a proteasome inhibitor and an IMiD). The purpose of this model was to create a framework to assess the cost of therapy and cost per 12 months of PFS, and was not intended to compare directly the efficacy of various treatment regimens.

Second, the model assumes patient adherence to therapy over the course of the median duration of therapy; gaps in treatment resulting from toxicities and drug "holidays" are not included; however, in using the median duration of therapy, any potential impact of discontinuation is implicitly accounted for. The rates for grade 3 or 4 adverse events are taken from either the drug labeling or from clinical trial results and are standardized to a monthly percentage to facilitate comparison across the treatment regimens. It is assumed that adverse events occur uniformly throughout the treatment duration (ie, adverse events are equally likely at any week of therapy).

To account for these limitations, we have used the median PFS and the median duration of therapy. By using

the median, patients who discontinue therapy either early or late as a result of adverse events have been accounted for as the median, in contrast to the mean, because a measure of central tendency is less reflexive to outliers.

In addition, for modeling purposes, the patients were assumed to be treated for the number of months necessary to achieve 12 months of PFS based on the median PFS and the median duration of therapy reported in the literature. This calculation is explicitly not intended to suggest that treating an individual patient for a shorter or longer period than recommended is appropriate and/or will result in linear gains in PFS in clinical practice.

Finally, on disease progression, the model assumes that patients return to their original treatment regimen. Although physicians and some clinical guidelines recommend that patients should be retreated with the same treatment regimen if they do not have refractory disease,^{10,41} this may not always reflect the individualized patient treatment pathways that are used in real-world practice. However, the ability to model detailed treatment pathways, as they relate to very specific patient profiles, is limited by the availability of data.

Conclusion

The present study represents the first treatment regimen cost estimator developed to comprehensively project the costs of managing patients with RRMM with all currently approved and recommended regimens in the United States, as of 2015. As such, our study provides the framework and basis for further budget impact analyses and for cost-effectiveness comparisons with the regimens included in this analysis. ■

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STAKEHOLDER PERSPECTIVE



The Rationale for Comparing the Costs of Competing Treatment Options in Oncology

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PAYERS: Historically, health plans have not focused a lot of attention on the cost of cancer treatments, regardless of disease stage or severity. The primary reasons for this lack of focus and management have been restrictive legislative mandates, the emotional nature of cancer treatments, and the lack of reasonable clinical alternatives for these difficult cases. Multiple myeloma is no exception to this rule, because of the complex nature of the disease and the significant variation in treatment approaches by oncologists in this particular type of cancer.

The lack of a recognized standard of care in the treatment of multiple myeloma makes any consideration of management a challenge to operationalize.¹ The need to effectively identify the clinical differences among the various treatments is typically left to the treating oncologist; however, cost is not usually considered as part of this process. In their current article in this issue of *American Health & Drug Benefits*, Dr Roy and colleagues provide a very interesting perspective that allows for an informed review of the cost differences among competing treatment options for relapsed or refractory multiple myeloma.²

The recent approvals of a number of new therapies to treat multiple myeloma, including panobinostat, poma-

lidomide, and carfilzomib, increase the need for sound clinical and financial reviews of the potential treatment options and the myriad of possible combinations that may be offered to patients.³ Although multiple myeloma represents approximately 1% of the cancer population, the cost of the various regimens makes multiple myeloma one of the most expensive cancers to treat for the typical health plan.^{4,5}

The evaluation of a number of treatment approaches using 12 months of progression-free survival as the target for comparing regimens is a reasonable approach. The use of wholesale acquisition cost (WAC) pricing eliminates any confusion or upcharges seen when average wholesale price is used in an analysis. Health plans do not typically receive any price concessions from drug manufacturers for oncologics, which further supports a WAC-based analysis. It was important for these researchers to include all of the potential costs of treatment, including for grade 3 or 4 side effects and other disease-related costs outside of the individual drug costs.²

RESEARCHERS/PAYERS: The challenge for health plans is to apply the learning from this research, and to make an effort to assess treatment costs in clinical

STAKEHOLDER PERSPECTIVE *Continued*

practice. As pointed out by the authors, clinical trial experience is a good starting point for this analysis²; however, real-world evidence is needed to effectively validate the results. Adherence to therapy is critical to achieve success, and the compliance rates in clinical trials are usually quite good.

PATIENTS: Most health plans note a significant decrease in adherence from clinical trials to real practice, and strategies to improve or maintain adherence are needed, and are often driven through specialty pharmacy providers who often supply the self-administered drugs to these patients under restricted network distribution arrangements with health plans.

MANAGED MARKETS: The type of cost analysis presented in this article is critical to the management of future oncology treatments in managed care markets. The improvements in information technology at health plans, including data warehouses that combine all the critical data elements to perform intelligent analyses of

all disease states, will support additional research on the true costs of managing patients with all types of cancer. The significant differences—as much as \$100,000—among the treatment options for multiple myeloma reviewed in this research will lead to additional data extraction and analysis by health plans that are looking to apply this research to pharmacy practice. ■

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